56. (amended) The method of claim 1, wherein said detection probe comprises at least one DTPA molecule wherein said multispecific molecule in said antigen-multispecific molecule-probe complex interacts with said diethylenetriaminepentaacetate (DTPA) molecule.

C6

REMARKS

Claims 1-25 and 56 are pending. Claims 1-4, 11, and 56 have been amended to more particularly point out and distinctly claim the invention and to place the claims in condition for allowance. Claim amendments are fully supported by the instant specification, thus, no new matter has been introduced.

A marked up versions of the amended paragraph and claims showing the amendments are attached hereto as Appendices A and B respectively. Matter that has been deleted is indicated by brackets and matter that has been added is indicated by underlining. A copy of the claims as pending after entry of the foregoing amendment is attached as Appendix C.

Claim Objection

Claim 11 has been objected to by the Examiner. Accordingly, Applicants have amended the claim to address the Examiner's objection.

The Rejections Under 35 U.S.C. §112

Claims 1-25 and 56 are rejected under 35 U.S.C §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner alleges that recitation of the phrases "imparted by" in claim 1, "associated with" in claims 3-4, and "DTPA" in claim 56 is unclear. Without in any way conceding that these phrases are unclear, and for the sole purpose of expediting prosecution of this application, Applicants have amended the claims as suggested by the Examiner. Accordingly, Applicants request that the Examiner withdraws the rejections under 35 U.S.C. §112.

The Rejections Under 35 U.S.C. §103

Claims 1, 16-25 and 56 are rejected under 35 U.S.C. §103(a) as being unpatentable over Griffiths (U.S. Patent No. 5,482,698) in view of Torchilin (*Critical Review in Therapeutic Drug Carrier Systems*, 1991, 7:275-308) and in further view of Bosslet (U.S. Patent No. 5,591,828). Furthermore, the Examiner also alleges that the present invention is obvious in view of Hansen (U.S. Patent No. 5,851,527) in view of Torchilin and in further view of Bosslet. Applicants respectfully disagree.

Conventional immunoassays known in the art use a monospecific antibody to recognize the antigen to be detected. This antibody may be covalently attached to a detection molecule or molecules or may serve as an antigen for and be bound by a second monospecific antibody which is covalently attached to a detection molecule or molecules (see Panel A of Exhibit 1). In either case, the detection molecule or molecules are attached to an antibody *prior to* that antibody recognizing its antigen. Because covalent attachment of a moiety to a protein may alter its secondary and/or tertiary structure (*e.g.*, many detection molecules are highly charged), attachment of such an entity to an antibody may affect the binding properties of the antibody and thus alter or impede antigen recognition.

The present invention is drawn to methods and compositions relating to the detection of very small quantities of a substance utilizing a bispecific antibody and a polymer probe. The multispecific molecule (*e.g.*, multispecific antibody) comprises at least two antigen binding regions with distinct specificities. The first antigen binding region recognizes an antigen to be detected and the second antigen binding region recognizes an antigen not endogenously found in the sample (*e.g.*, DTPA). The first and second antigen binding regions may be on different molecules (*e.g.*, at least two antibodies of different antigen binding specificities linked together, each antibody having an antigen binding region on each arm that binds the same antigen; see the left-hand figure in Panel B of Exhibit 1) or the same molecule (*e.g.*, a single antibody that has a different antigen binding region on each arm; see the right-hand figure in Panel B of Exhibit 1). A polymer probe is conjugated to the non-endogenous antigen as well as more than two detection molecules (*e.g.*, horse radish peroxidase).

In contrast to previously described methods, the assay is performed in the following steps. First, the multispecific molecule is contacted with a sample that may contain an antigen to be detected. Incubation time is given to allow the multispecific molecule to bind to the antigen to be detected should the antigen be present in the sample. Second, the polymer probe is contacted with the complex of the multispecific molecule

bound to the antigen to be detected. Detection molecules are then visualized to indicate the presence and quantity of the antigen to be detected. This unique two step process allows the antigen binding region which detects the antigen of interest in the sample to bind in the absence of the non-endogenous antigen and/or the label molecules. This key difference with conventional methods has allowed the present inventors to shown that they are able to improve detection of small quantities of antigens by more than 1,000 times over currently used protocols.

Griffiths discloses a method for detecting or treating lesions in a patient *in situ*. An antibody is injected into a patient which localizes to the lesion to be detected or treated (*i.e.*, a tumor). This antibody is covalently linked to a biotin molecule or polymer containing biotin molecules (*i.e.*, the antigen binding region is binding to the antigen of interest in the presence of biotin). Subsequently, avidin is injected into the patient and binds to the biotin. In a final step, biotin conjugated to a detection or therapeutic molecule is injected into the patient and binds to the avidin (see Panel C of Exhibit 1). Although Griffiths does disclose "bispecific antibodies", the term is used to describe a protein that is not contemplated in the instant application. Specifically, Griffiths teaches using a hybrid antibody whereby the antibody arms are directed against different epitopes of the same antigen or against different substances associated with the lesion (see *e.g.*, column 7, lines 37-41 and column 10, lines 13-24). This is done to increase the targeting efficiency of the antibody. Nowhere in the Griffiths does it teach using the antibody to recognize a detection molecule or an epitope conjugated to a detection molecule.

Torchilin is a review discussing protein modification with chelating polymers. In particular, preparation of labeled monoclonal antibodies is highlighted. All of the antibodies disclosed are *monospecific* and *directly* conjugated to another moiety – either a detection molecule or a polymer containing the detection molecule (see Panel D of Exhibit 1). This type of direct conjugation is exactly what the instant specification teaches away from. Additionally, the DTPA-derivatized polylysine of Figure 8 is directly conjugated to the antibody. In the instant application, the DTPA-containing polymer is free in solution and not linked to anything. The second antibody binds to the DTPA as an epitope thus relieving the requirement for covalent linkage and the alteration of antibody specificity.

Bosslet discloses a hybrid molecule consisting of two F(ab) fragments of antibodies of two different specificities associated by means of a linker. A F(ab) fragment is a small portion of an antibody that retains its ability to bind antigen (see Panel E of

Exhibit 1). This is qualitatively different from having the antigen binding region of an antibody in the context of a complete antibody molecule. Additionally, the hybrid molecule of Bosslet is made up of a portion of an antibody that binds to an antigen of interest and a portion of an antibody that binds a detection or therapeutic molecule complex. In one embodiment, the second antibody binds to DTPA labeled with a metal ion. There is no teaching that DTPA can be complexed to a polymer probe that also contains detection molecules.

Hansen discloses a method for targeting a therapeutic agent to a particular site in a patient *in situ*. An antibody is injected into a patient that targets to a particular site. In addition to simply targeting, the antibody also is responsible for bringing an enzyme to the site as well (*i.e.*, the antigen binding region is binding to the antigen of interest in the presence of a covalently attached enzyme). The substrate for this enzyme is also injected into the patient. A particular feature of this enzyme/substrate pair is that, once the substrate is metabolized by the enzyme, there is an insoluble product. By conjugating a therapeutic agent to the substrate, one can target therapeutic agent accumulation at the site where the antibody binds to its antigen (this scheme is depicted in Panel F of Exhibit 1).

A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and the content of the prior art, the differences between the invention and the prior art, the level of the ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether one of ordinary skill in the art would have had a reasonable expectation that the claimed invention would be successful. *In re O'Farrell*, 853 F.2d 894, 902-4 (Fed. Cir. 1988); *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988).

Furthermore, Applicants submit that any rejection of the pending claims under §103 would indicate the improper use of hindsight gained from Applicants' own specification. Hindsight should be avoided in applying the nonobviousness requirement. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987), *cert. denied*, 481 U.S. 1052 (1987). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988).

Without the benefit of hindsight, the teachings of the references cited by the Examiner, alone or in combination, could not render obvious the claimed invention. The claimed compositions and methods could not have been foreseen by a person of ordinary skill in the art, since there was no suggestion of them in the art and their utility for immunoassays could not have been predicted. A finding of obviousness could only be arrived through a prohibited procedure in which "the claims were used as a frame, and individual naked parts of separate prior art references were employed as a mosaic to recreate a facsimile of the claimed invention." *W.L. Gore & Assocs. Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552, 220 U.S.P.Q. 303, 312 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Applicants respectfully submit that for all the reasons discussed above, the references cited by the Examiner do not teach or suggest the claimed invention. In view of the foregoing, Applicants request that the Examiner withdraws the rejection under 35 U.S.C. § 103(a).

CONCLUSION

Entry of the foregoing amendments and remarks into the file history of the above-captioned patent application is respectfully requested. Applicants believe that the foregoing amendments and remarks place the claims in condition for allowance. Withdrawal of all rejections and reconsideration of the amended claims is respectfully requested. An allowance is earnestly sought.

Respectfully submitted, by: Milton A. Wenk
Reg. No. 53,759

Date: March 19, 2003

Berj A. Terzian 20,060
Berj A. Terzian (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, N.Y. 10036-2711
(212) 790-9090

APPENDIX A

MARKED-UP COPY OF THE AMENDED PARAGRAPH
U.S. PATENT APPLICATION SERIAL NO. 09/727,421
ATTORNEY DOCKET NO. 9449-016-999

This application is a continuation-in-part of United States Patent Application Serial No. 09/380,168, filed October 6, 1999, which is the national stage application of International [Publication No. WO 98/38513] Patent Application PCT/US98/03638, filed February 25, 1998, which claims the benefit of priority to U.S. Provisional Application No. 60/039,111 filed February 26, 1997, the contents of each of which are incorporated herein by reference in their entirety.

APPENDIX B
MARKED-UP COPY OF THE AMENDED CLAIMS
U.S. PATENT APPLICATION SERIAL NO. 09/727,421
ATTORNEY DOCKET NO. 9449-016-999

1. A method of detecting an antigen of interest in a sample comprising:

contacting the sample with a multispecific molecule, said multispecific molecule being capable of simultaneously binding the antigen of interest and a labeled detection probe, and allowing an antigen-multispecific molecule complex to form;

contacting the sample with a labeled detection probe, wherein said detection probe comprises at least two molecules of a detectable label, for sufficient time to form an antigen-multispecific molecule-probe complex; and

detecting the labels [imparted by] of the [labeled detection probe to the] antigen-multispecific molecule-probe complex.

2. The method of claim 1, wherein said antigen of interest is selected from the group consisting of a drug [antigens] antigen, a tumor [antigens] antigen, a viral [antigens] antigen, a bacterial [antigens] antigen, a [hormones] hormone, a plasma [proteins] protein, a plaque [antigens] antigen, a [haptens] hapten, and a [steroids] steroid.

3. The method of claim 2, wherein said tumor antigen is [associated with] a breast, prostate, brain, liver, kidney, colon, pancreatic, stomach, or lung cancer tumor antigen.

4. The method of claim 2, wherein said viral antigen is a [antigens are associated with] hepatitis type A, hepatitis type B, hepatitis type C, influenza, varicella, adenovirus, herpes simplex virus type I (HSV-I), herpes simplex virus type II (HSV-II), rinderpest, rhinovirus, echovirus, rotavirus, respiratory syncytial virus, papilloma virus, papova virus, cytomegalovirus, echinovirus, arbovirus, hantavirus, coxsachie virus, mumps virus, measles virus, rubella virus, polio virus, human immunodeficiency virus type I (HIV-I), [and] human immunodeficiency virus type II (HIV-II), picornaviridae, [enteroviruses] enterovirus, caliciviridae, Norwalk [viruses] virus, Dengue virus, [alphaviruses] alphavirus, [flaviviruses] flavivirus, [coronaviruses] coronavirus, rabies virus, Marburg [viruses] virus, ebola [viruses] virus, parainfluenza virus, [orthomyxoviruses] orthomyxovirus, [bunyaviruses] bunyavirus, [arenaviruses] arenavirus, [reoviruses] reovirus, [rotaviruses]

rotavirus, [orbiviruses] orbivirus, human T cell leukemia virus type I, human T cell leukemia virus type II, simian immunodeficiency virus, [lentiviruses] lentivirus, [polyomaviruses] polyomavirus, [parvoviruses] parvovirus, Epstein-Barr virus, human herpes virus-6, cercopithecine herpes virus 1 (B virus), [and] or poxvirus viral antigen [poxviruses].

11. The method of claim 10, wherein said sample [from a human patient] is [a] tissue, blood, saliva, urine, or plasma from a human patient [sample].

56. The method of claim 1, wherein said detection probe comprises at least one DTPA molecule wherein said multispecific molecule in said antigen-multispecific molecule-probe complex interacts with said diethylenetriaminepentaacetate (DTPA) molecule.